Introduction to mediation analysis

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Imperial College, 15 May 2014

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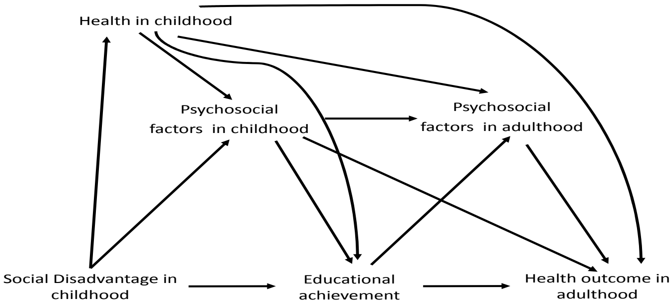
- In other words we are interested in the study of mediation.

Example: mediation in life course epidemiology

Focus on distal exposures for later life outcomes:



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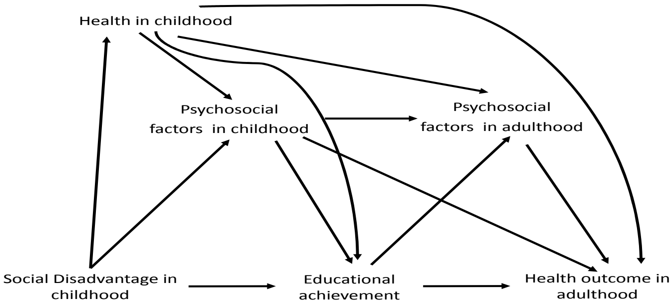

Interest: disentangle the underlying processes.

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- Is cognitive behaviorial therapy acting via increased compliance in reducing suicide rates?
- Is the effect of tamoxifen on CVD mediated/modified by other drugs taken to control its symptoms?

The study of mediation

- Two main strands in the literature for the study of mediation:
  - Social sciences / psychometrics (Baron and Kenny, 1986)
  - Causal inference literature (Robins and Greenland, 1992; Pearl, 2001)
- The first more accessible, but also misused/misunderstood
- The second more rigorous and general, but more complex

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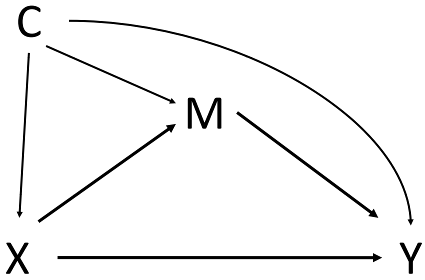
Aims:

- outline these two approaches
- compare them and show important differences
- show an application

Outline

Simplify the question: one mediator

Exposure X, mediator M, outcome Y and confounders C.



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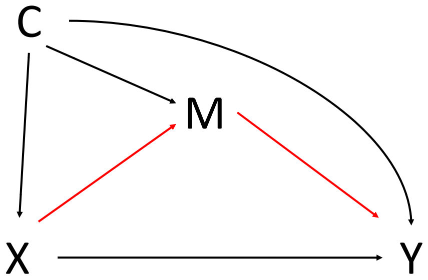

Simplify the question: one mediator

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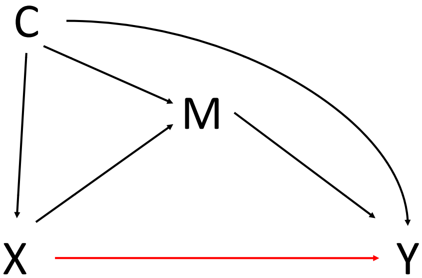
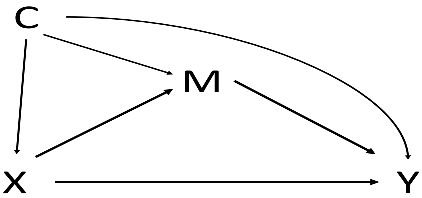
Mediation leads to separate the two pathways: indirect and direct.



Outline

A Simple linear Structural Equation Model (LSEM) (1)



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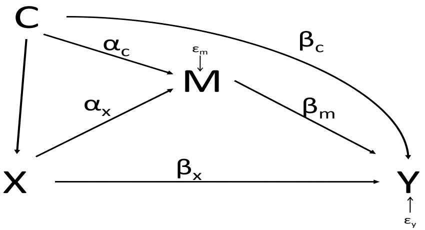
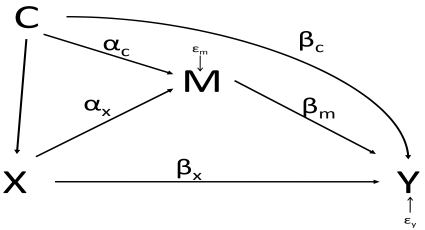


Consider the LSEM corresponding to this diagram:

$$\begin{cases} M = \alpha_0 + \alpha_x X + \alpha_c C + \epsilon_m \\ Y = \beta_0 + \beta_x X + \beta_m M + \beta_c C + \epsilon_y \end{cases} \tag{1}$$

ϵ_m and ϵ_y uncorrelated error terms, also uncorrelated with the explanatory variables in their equations.

A Simple linear Structural Equation Model (LSEM) (2)



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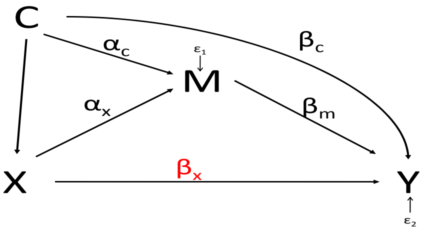

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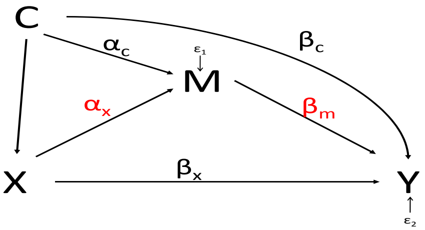

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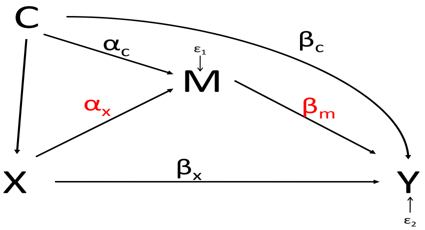

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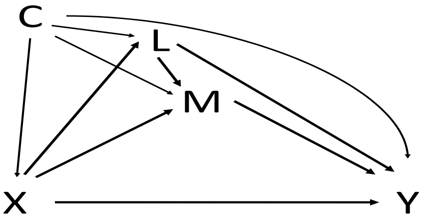
Estimation via ML/OLS; delta method/ bootstrapping to obtain SEs for the indirect effect.

Intermediate confounders (1)



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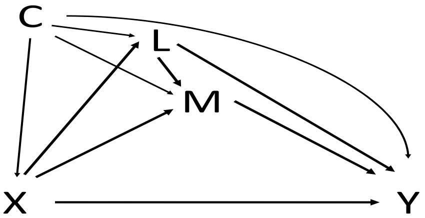

Here L is an intermediate confounder (endogenous variable) because it is influenced by X. If L is a continuous variable:

$$\begin{cases} L = \gamma_0 + \gamma_x X + \gamma_c C + \epsilon_l \\ M = \alpha_0 + \alpha_x X + \alpha_l L + \alpha_c C + \epsilon_m \\ Y = \beta_0 + \beta_x X + \beta_m M + \beta_l L + \beta_c C + \epsilon_y \end{cases} \quad (2)$$

ϵ_l, ϵ_m, and ϵ_y uncorrelated error terms, also uncorrelated with the explanatory variables in their equation.

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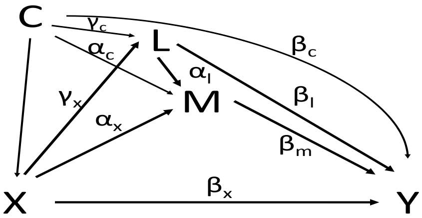

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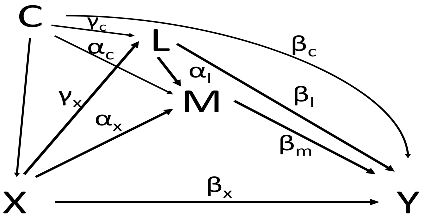

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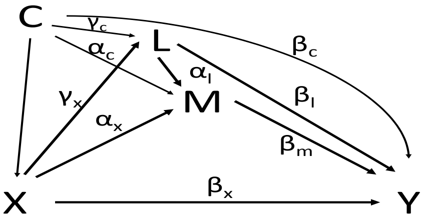

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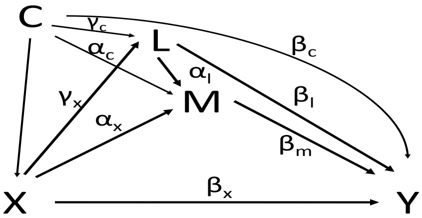

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- Effect mediated via M, the indirect effect is $(\alpha_x\beta_m + \gamma_x\alpha_l\beta_m)$
- Effect not mediated by M, the direct effect: $(\beta_x + \gamma_x\beta_l)$

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- Extension to the case with intermediate confounder L is straightforward
- Models can only be linear for Y, M and L, with no interactions nor other non-linearities (*e.g.* M^2)
- Derivations of direct and indirect effects are always specific to a particular model
- For non-linear settings: approximate solutions (and for defining indirect effects only (Hayes and Preacher, 2010))

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- Explicitly aiming for causal statements, this approach invokes the notion of *"how the world would have been had something been different"*
- Hence use of quantities that are not all observable: *potential outcomes* and the *potential mediators*.

Potential outcomes

- $Y(x)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x.
- $M(x)$: the potential values of M that would have occurred had X been set, possibly counter to fact, to the value x.
- $Y(x, m)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x and M to m.

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> - For simplicity consider the case where X is binary
> - It also helps to start with the definition of *total causal effect*

Total Causal Effect (TCE): definition

The average total causal effect of X, comparing exposure level $X = 1$ to $X = 0$, can be defined as the linear contrast [1]:

$$TCE = E[Y(1)] - E[Y(0)]$$

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In general: $TCE \neq E[Y|X = 1] - E[Y|X = 0]$
hence TCE cannot be naively estimated from the data.

Total Causal Effect (TCE): identification

To identify TCE we need to infer $E[Y(1)]$ and $E[Y(0)]$ from the data.

This is possible under certain assumptions. Those most invoked are:

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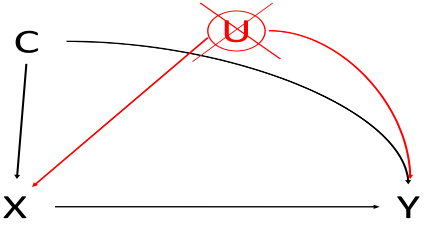

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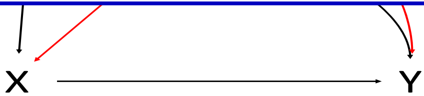
If these are satisfied, we can infer the TCE from the data

$$\sum_c \{E(Y|X=1, C=c) - E(Y|X=0, C=c)\} Pr(C=c)$$



Controlled Direct Effect (CDE): definition

The average controlled direct effect of X on Y, when M is controlled at m, is:

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- In general $CDE(m)$ varies with m

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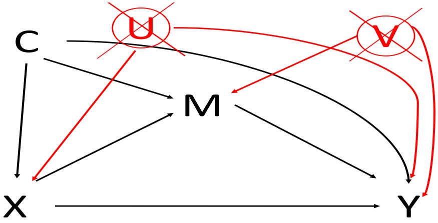

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If these assumptions are satisfied we can infer the $CDE(m)$ from the observed data

$$\sum_c \{E(Y|X=1, M=m, C=c) - E(Y|X=0, M=m, C=c)\}$$

$$Pr(C=c)$$

Pure Natural Direct Effect (PNDE): definition

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- In both worlds, M is set to the natural value $M(0)$, *i.e.* the value it would take if X were set to 0.
- Since M is the same (*within* individual) in both worlds, we are still getting at the direct effect of X, unmediated by M.

Pure Natural Direct Effect: identification

Identification possible, as before, under extensions of the earlier assumptions:

(i) no interference

(ii) consistency, extended to include:
$Y = Y(x, m)$ if $X = x$ and $M = m$, $M = M(x)$ if $X = x$, and
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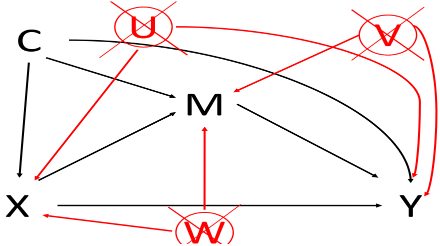

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> If these assumptions are satisfied: we can infer the NDE from the observed data

Total Natural Indirect Effect (TNIE): definition

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This is a comparison of two hypothetical worlds: In both X is set to 1, while M is set to the natural value when X is set to 1 or 0.

The same assumptions as for $PNDE$ are required to identify the $TNIE$.

The identification equations

- Each of these estimands can be identified under certain assumption and via an identification equation, *e.g.*

$$CDE(m) = \sum_{c} \{E(Y|X=1, M=m, C=c) - E(Y|X=0, M=m, C=c)\} Pr(C=c)$$

$$PNDE = \sum_{c} \left\{ \sum_{m} \{E(Y|X=1, M=m, C=c) \; - \; E(Y|X=0, M=m, C=c)\} \right.$$
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- These equations can be extended to deal with continuous M and C and to include intermediate confounders L.
- Their essence is the specification of conditional expectations of Y, conditional distributions for M (and L) (and marginal distributions for C).

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Wide range of options, for most combinations of M and Y:

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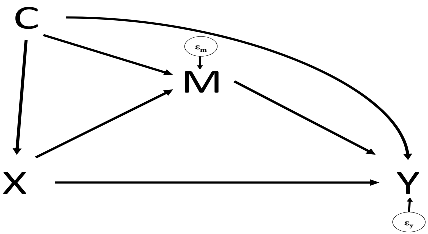
  - It is the direct implementation of the identification equations
  - requires correct specification of all relevant conditional expectations and distributions
  - implemented in `gformula` command in Stata
- Semi-parametric methods make fewer parametric assumptions:
  - Inverse probability of treatment weighting (IPTW):
    - not practical when M is continuous
  - Various flavours of G-estimation
    - generally more complex to understand

Outline

Revisiting SEMs

Structural assumptions with no intermediate confounders



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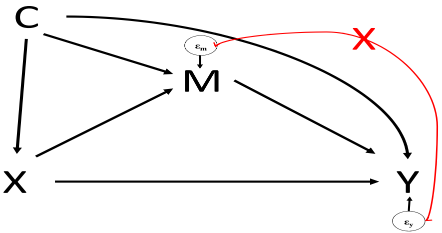

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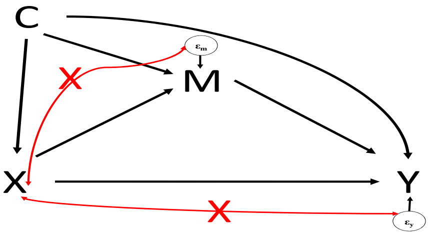

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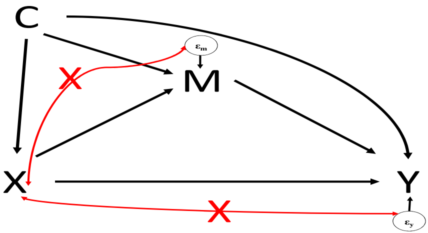

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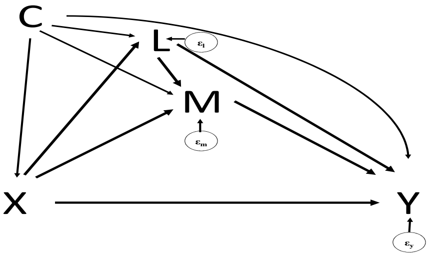
'Same' as no unaccounted common causes for $M - Y$, $X - Y$, $X - M$.

Revisiting the SEM assumptions (2)

Structural assumptions with intermediate confounders



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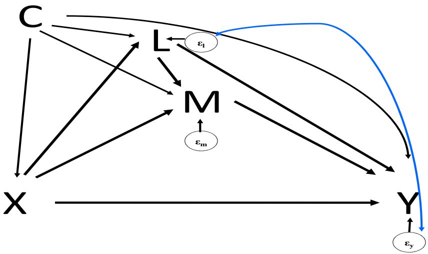

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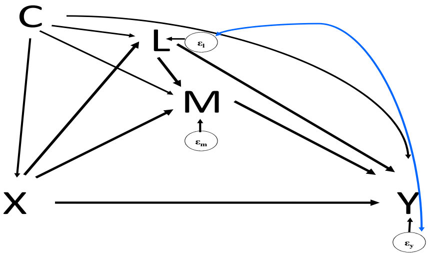

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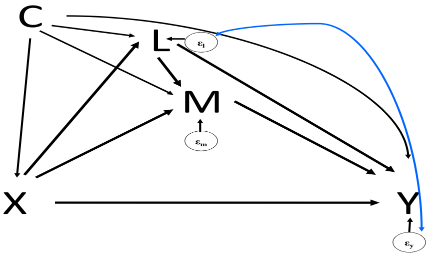

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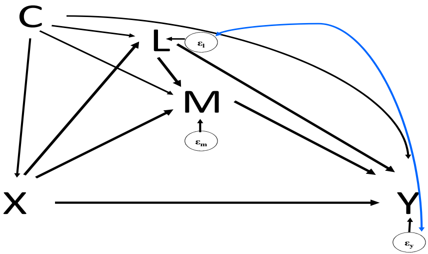

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> With linear models, structural assumptions for mediation analysis from the two schools are essentially equivalent

Revisiting the SEM assumptions (3)

Parametric assumptions

If a structural model is linear and does not include interactions or other non-linear terms:

- identifying equation for modern causal inference would lead to same estimands as adopting an SEM approach:
  - $CDE(m) = PNDE = \beta_x$
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> Estimation-by-combination

Estimation-by-combination

Consider a more general linear SEM:

$$\begin{cases} L = \gamma_0 + \gamma_x X + \gamma_c C + +\epsilon_l \\ M = \alpha_0 + \alpha_x X + \alpha_l L + \alpha_c C + \epsilon_m \\ Y = \beta_0 + \beta_x X + \beta_l L + \beta_m M + \beta_{mm} M^2 + \beta_c C + \beta_{xm} XM + \epsilon_y \end{cases}$$

Applying the appropriate identification equations leads to:

$$\begin{aligned} \text{CDE(m)} &= \beta_x + \beta_l \gamma_x + \beta_{xm} m \\ \textit{PNDE} &= \beta_x + \beta_l \gamma_x + \beta_{xm} \left[\alpha_0 + \alpha_l \left(\gamma_0 + \gamma_c \overline{C}\right) + \alpha_c \overline{C}\right] \\ \text{TNIE} &= \left(\beta_m + \beta_{xm}\right)\left(\alpha_x + \gamma_x \alpha_l\right) + \\ &\quad \beta_{mm} \left[\left(\alpha_x + \gamma_x \alpha_l\right)^2 + 2\left(\alpha_x + \gamma_x \alpha_l\right)\left(\alpha_0 + \alpha_l \left(\gamma_0 + \gamma_c \overline{C}\right) \right.\right. \\ &\quad \left.\left. + \alpha_c \overline{C}\right)\right] \end{aligned}$$

where each of these parameters can be estimated by the model above, leading to the same results as from g-computation.

Comparison of G-computation and estimation-by-combination

Scenario	Method	PNDE estimate	PNDE (s.e.)	TNIE estimate	TNIE (s.e.)	CDE(0) estimate	CDE(0) (s.e.)
Y, M, with C, MX	true	0.730	-	0.240	-	0.400	-
	g-estimation	0.731	(0.003)	0.238	(0.003)	0.405	(0.003)
	combination	0.731	(0.002)	0.239	(0.001)	0.405	(0.003)
Y, M, with MX and M^2	true	0.730	-	0.344	-	0.400	-
	g-estimation	0.730	(0.004)	0.341	(0.004)	0.406	(0.003)
	combination	0.731	(0.002)	0.342	(0.002)	0.406	(0.003)
Y, M, L, with MX, M^2	true	0.806	-	0.787	-	0.520	-
	g-estimation	0.806	(0.007)	0.783	(0.008)	0.527	(0.004)
	combination	0.807	(0.002)	0.783	(0.003)	0.527	(0.004)
Y, M,L, with C, U	true	0.520	-	0.156	-	0.520	-
	g-estimation	0.521	(0.003)	0.158	(0.003)	0.521	(0.004)
	combination	0.520	(0.002)	0.157	(0.001)	0.520	(0.002)

Datasets of size=1,000,000 generated according to specified model with $N(0, 1)$ errors and binary C ($p = 0.5$).

Standard errors obtained via bootstrap for g-computation and the delta method for estimation-by-combination.

Comparison: summary

With continuous endogenous variables represented by a recursive linear system:

- structural assumptions for mediation made by the two approaches closely related, even in the presence of intermediate confounders
- fully parametric estimation via g-computation is achievable within an SEM framework, even in the presence of interactions and other non-linearities, and even if there is unmeasured $L - Y$ confounding.

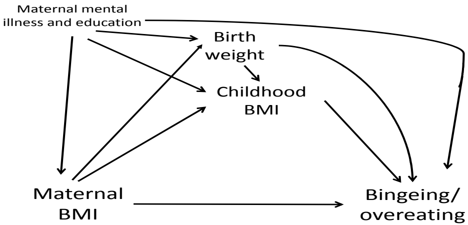
Outline

Eating disorders (ED) in adolescence

Work in progress: girls in ALSPAC, birth cohort 1991-2

- ED comprise a variety of heterogeneous diseases
- Maternal factors possibly important
- Childhood BMI a possible mediator
- Data:
  - Outcome: ED scores derived from parental questionnaire on the child's psychological distress when aged 13.5y: today focus on *"Binge eating"*
  - Exposure: pre-pregnancy maternal BMI (binary, $> 25\text{kg/m}^2$)
  - Mediator: Childhood BMI (around age 7, age-standardized)
  - Confounders: pre-pregnancy maternal mental illness, maternal education, girl's birth weight

Maternal BMI, childhood BMI and eating disorders



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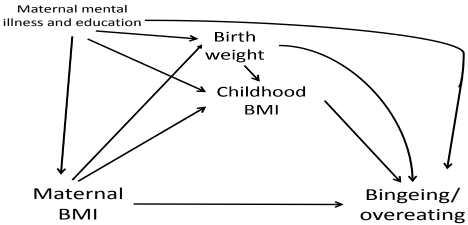

The causal question

How much of the effect of maternal BMI on her daughter's ED score is due to its effect on the child's BMI?

More specifically . . .

We can ask either of these question:

> What effect does intervening on maternal BMI have on later ED if we could also intervene on each child BMI and set it to a particular level?

- Controlled Direct Effect

> What effect does intervening on maternal BMI has on later ED in a world where the effect of maternal BMI has no effect on her child BMI?

- Natural Direct Effect

Identification

Identification requires assumptions that allows us to use observed data to derive potential outcomes. According to the estimand, varying specifications of:

(i) no interference

(ii) consistency

(iii) no unmeasured confounding

(iv) for PNDE and TNIE: some parametric restrictions

Maternal BMI, childhood BMI and eating disorders

Results from g-computation and estimation-by-combination

Model	Estimand	G-computation Estimate	G-computation (s.e.)	Combination Estimate	Combination (s.e.)
Model 1: no X–M interaction					
	TCE	0.287	(0.049)	0.287	(0.052)
	PNDE	0.103	(0.047)	0.102	(0.050)
	TNIE	0.184	(0.019)	0.185	(0.021)
Model 2: *CDE*(m) does not vary with $M(0)$					
	TCE	0.297	(0.047)	0.297	(0.049)
	PNDE	0.102	(0.051)	0.103	(0.051)
	TNIE	0.195	(0.026)	0.194	(0.028)

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Which of these models is best?

Maternal BMI, childhood BMI and eating disorders

Structural model for Bingeing/Overeating

Expl. var.	Model 1 No $X-M$ interaction Estimate	 (s.e.)	Model 2 No $X-L$ nor L^2 Estimate	 (s.e.)	Model 3 No constraints Estimate	 (s.e.)
X	0.072	(0.048)	0.084	(0.049)	0.068	(0.050)
M	0.315	(0.019)	0.313	(0.021)	0.312	(0.021)
M^2	0.044	(0.012)	0.042	(0.012)	0.043	(0.012)
L	0.034	(0.022)	0.054	(0.020)	0.034	(0.022)
L^2	0.032	(0.012)	-	-	0.032	(0.012)
XL	0.078	(0.045)	-	-	0.078	(0.045)
XM	-	-	0.017	(0.045)	0.014	(0.045)
C_1	-0.011	(0.036)	-0.011	(0.036)	-0.011	(0.036)
C_2	0.207	(0.054)	0.209	(0.054)	0.207	(0.054)

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  (b) While modern causal inference focuses on summary effects, SEMs help closer examination of specifications (novel semi-parametric approaches should not however be overlooked!).

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- For a linear recursive system, can estimate causal estimands using SEMs.
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  (b) While modern causal inference focuses on summary effects, SEMs help closer examination of specifications (novel semi-parametric approaches should not however be overlooked!).
- Thank you!

References

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